Remarks

Applicants respectfully request that this application be reconsidered in view of the above amendments and the following remarks.

1. Status of the Claims

Claims 20-26, and 28-30 were pending in this application of which Claims 28-30 were withdrawn from consideration. In this response, Claims 20 and 28 have been amended, Claim 21 has been canceled, and new Claims 41-43 have been added. Accordingly, Claims 20, 22-26, 28-30, and 41-43 remain pending in this application, of which Claims 28-30 and 43 stand withdrawn.

2. Support for the Amendments

The amendment to Claim 20 incorporates the subject matter of Claim 21 into Claim 20 and further distinctly claims the subject matter which Applicants regard as their invention. Additional support for the amendment to Claim 20 and for new Claims 41 and 42 is found in the specification at page 8, lines 8 to 10, at page 9, lines 12-16, and at page 22, line 13 to page 23, line 5. Support for new Claim 43 is found at least at page 9, line 2. Withdrawn Claim 28 has been amended to recite a process for preparing the pharmaceutical composition of Claim 20, thus emphasizing the eligibility of Claim 28 for rejoinder upon a finding of allowability of Claim 20. No new matter has been added. Entry of the amendments is respectfully requested.

3. Rejection of Claims 20-26 under 35 U.S.C. §103(a)

Claims 20-26 were rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of Moran et al. (US 6,576,793 B1) and Patton (US 5,607,915).

As required by M.P.E.P. §2143, to establish a *prima facie* case of obviousness, the Examiner must at least show (1) that the prior art reference teaches or suggests all the claim limitations, (2) that there is some suggestion or motivation, either in the reference or in the knowledge available to one of ordinary skill in the art, to modify the reference, and (3) that there is a reasonable expectation of success.

Applicants traverse this rejection because the Examiner has failed to meet the requirements for a *prima facie* showing of obviousness.

Claim 20, as amended, recites a pharmaceutical composition comprising *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine dihydrochloride; a buffering agent; and water; wherein the buffering agent is present in an amount sufficient to maintain the composition at a pH in the range of about 5 to about 5.5 and wherein the composition is stable upon storage. Claim 20 has five distinct elements: (1) the specific chemical compound; (2) that the compound be present as its dihydrochloride salt; (3) a buffering agent present in an amount sufficient to maintain the composition in a specified pH range; (4) water; and (5) that the composition is stable upon storage. Claim 22 recites that the buffering agent comprises a citrate species. Claim 23 recites the limitation that the composition is isotonic. Claims 41 and 42 recite specific stability limitations.

Moran '793 does not teach or suggest a pharmaceutical composition with the limitations of Claim 20 and claims dependent therefrom. In the first place, nowhere does Moran '793 disclose the dihydrochloride salt of the present compound, neither in Fig. 15 compound 72, nor in Example 12. Secondly, nowhere does Moran '793 disclose a buffering agent. The Examiner has pointed to column 19, lines 49-50 as "expressly" teaching citric acid. Applicants respectfully submit the Examiner is not accurately interpreting the reference. At column 19, lines 43 to 53, Moran '793 recites a list of acids from which pharmaceutically acceptable addition salts may be derived. The inclusion of citric acid in such a list by no means constitutes a disclosure of a citrate species buffering agent present in a pharmaceutical composition in an amount sufficient to maintain the composition in a specific pH range. Accordingly Moran '793 does not teach or suggest all the claim limitations of Claim 20.

The Examiner noted that Moran '793 fails to teach an isotonic solution, citing Patton '915, column 5, line 55, and lines 62-66 as remedying this deficiency by expressly teaching that sodium chloride can be added to a pharmaceutical composition for a nebulizer. Applicants respectfully submit the Examiner is misinterpreting this reference, as well. Patton '915 is directed to formulations for pulmonary delivery of parathyroid hormone (PTH), an 84 amino acid protein, and to 34 or 38 amino acid fragments thereof. The word "sodium chloride" at column 5, line 55 appears in a passage disclosing means

of stabilizing PTH fragments in solution prior to formation of particles for administration by dry powder devices. The passage is **not** directed to a pharmaceutical formulation suitable for nebulizer administration. Specifically at lines 50 to 52, Patton '915 discloses"[t]ypically, suitable buffers and salts may be used to stabilize the PTH fragments in solution prior to particle formation" and goes on to include sodium chloride as one of the suitable salts. At lines 62 to 66 Patton discloses buffers for use in liquid formulations of PTH fragments. Accordingly, Patton does not teach an isotonic solution for nebulizer administration.

Thus, the references, even when taken together, do not teach or suggest all the claim limitations.

Furthermore, it is known that water is the preferred solvent for formulations suitable for nebulizer administration but that, in general, drug substances are less stable in aqueous media than in the solid dosage form. (*See* Remington: The Science and Practice of Pharmacy, 20th Edition, Lippincott Williams & Wilkins, Philadelphia, PA, (2000) p. 721). For example, U.S. 6,040,344, of record, identified stability of a pharmaceutical composition of formoterol tartrate, a different β_2 adrenergic receptor agonist, prepared for nebulizer administration, as a limitation to its acceptability.

The stability of an aqueous formulation may depend critically on, among other factors, the nature of the specific chemical compound, the particular salt form that is prepared, and the pH of the solution. Patton is directed to an 84, 34, or 38 amino acid protein or fragment, which clearly may be expected to have very different physical properties from those of the present "small molecule" pharmaceutical agent. Therefore, it is highly doubtful that any teaching of Patton would be applicable to the present case. A person skilled in the art would not look to Patton for guidance in preparing a nebulizer formulation of the present compound.

In summary, the references, even when taken together, do not teach or suggest all the claim limitations; the second reference, Patton, is not applicable in the present instance; and in view of the known problematic stability of drug substances in aqueous media, the art cited does not provide a reasonable expectation of success.

Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness. and the present rejection under 35 U.S.C. §103(a) should be withdrawn.

4. Conclusion

In view of the foregoing, Applicants respectfully submit Claims 20, 22-26, 41, and 42 are in condition for allowance. Further, upon allowance, according to *In re Ochiai* (71F. 3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) and MPEP §821.04, the restriction between Group I (Claims 20, 22-26, 41, and 42) and Group V (Claims 28-30 and 43), directed to the process of preparing the formulation of Claim 20 may be withdrawn.

Reconsideration of this application and prompt passage to allowance is respectfully requested. Should there be any issues regarding this application that may be resolved by telephone, the examiner is invited to telephone the undersigned agent for Applicants at (650) 808-3764 (direct).

Respectfully submitted,
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Date: April 18, 2008

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